Original Article

Risk assessment for postoperative venous thromboembolism using the modified Caprini risk assessment model in lung cancer

Yao Ding[1,2#], Lijun Yao[1#], Tao Tan[3#], Qiang Li[1], Haoming Shi[1], Yuan Tian[4], Aimée J. P. M. Franssen[5], Erik R. de Loos[5], Muteb Al Zaidi[6], Giuseppe Cardillo[7,8], Biniam Kidane[9], Konstantinos Grapatsas[10], Qingchen Wu[1], Cheng Zhang[1]

[1]Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; [2]Department of Thoracic Surgery, The People's Hospital of Kaizhou District, Chongqing, China; [3]Chongqing Health Statistics Information Center, Chongqing, China; [4]Department of Medical Affairs, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; [5]Department of Surgery, Division of General Thoracic Surgery, Zuyderland Medical Center, Heerlen, The Netherlands; [6]Thoracic and Upper GI Surgeon, Thoracic Surgery Unit, King Abdullah Medical City, Makkah, Saudi Arabia; [7]Unit of Thoracic Surgery, San Camillo Forlanini Hospital, Rome, Italy; [8]Unicamillus – Saint Camillus University of Health Sciences, Rome, Italy; [9]Section of Thoracic Surgery, University of Manitoba, Winnipeg, Manitoba, Canada; [10]Department of Thoracic Surgery, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany

Contributions: (I) Conception and design: C Zhang, Q Li; (II) Administrative support: Y Tian, Q Wu; (III) Provision of study materials or patients: Q Li, C Zhang; (IV) Collection and assembly of data: Y Ding, L Yao, T Tan, H Shi; (V) Data analysis and interpretation: Y Ding, L Yao, T Tan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Cheng Zhang, MD. Department of Cardiothoracic Surgery, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuanjiagang, Yuzhong District, Chongqing 400000, China. Email: chengzcqmu@163.com.

Background: Postoperative venous thromboembolism (VTE) is a well-documented cause of morbidity and mortality in lung cancer patients. However, risk identification remains limited. In this study, we sought to analyze the risk factors for VTE and verify the predictive value of the modified Caprini risk assessment model (RAM).

Methods: This prospective single-center study included patients with resectable lung cancer who underwent resection between October 2019 and March 2021. The incidence of VTE was estimated. Logistic regression was used to analyze the risk factors for VTE. Receiver operating characteristic (ROC) curve analysis was performed to test the ability of the modified Caprini RAM to predict VTE.

Results: The VTE incidence was 10.5%. Several variables, including age, D-dimer, hemoglobin (Hb), bleeding, and patient confinement to bed were significantly associated with VTE after surgery. The difference between the VTE and non-VTE groups in the high-risk levels was statistically significant (P<0.001), while the low and moderate risk levels showed no significant difference. The combined use of the modified Caprini score and the Hb and D-dimer levels showed an area under the curve (AUC) was 0.822 [95% confidence interval (CI): 0.760–0.855. P<0.001].

Conclusions: The risk-stratification approach of the modified Caprini RAM is not particularly valid after lung resection in our population. The use of the modified Caprini RAM combined with Hb and D-dimer levels shows a good diagnostic performance for VTE prediction in patients with lung cancer undergoing resection.

Keywords: Venous thromboembolism (VTE); lung cancer; the modified Caprini risk assessment model; risk factor

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Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide (1). Currently, surgery is regarded as the most reliable radical treatment for primary early-stage lung cancer. Among the various complications after lung surgery, thromboembolism requires serious attention because of its impact on morbidity and mortality (2,3). Postoperative venous thromboembolism (VTE) after lung resection as cancer treatment leads to a nearly eight-fold increase in mortality, which is higher than that reported for other cancer surgeries (4). Approximately 15% of cancer patients will experience VTE (5), and its incidence among different groups of cancer patients varies considerably depending on clinical factors (6). In non-cardiac chest surgery, the rate of thromboembolic complications can reach up to 12.1% (7-9). Hence, prevention is considered key in minimizing VTE-induced morbidity and mortality for lung cancer patients who receive surgery.

Although the overall risk of VTE is high in patients with lung cancer (3), risk identification remains limited. As a result, new strategies are necessary to identify patients who are at an increased risk of postoperative VTE. Risk assessment models (RAMs) have been developed to identify cancer patients at risk of VTE preoperatively and to target anticoagulation for the primary prevention of VTE. A multitude of RAMs for cancer-associated VTE have emerged in recent decades (10), and it is imperative for specialist clinicians to select the most appropriate VTE risk assessment score for specific cancer types. The Caprini RAM has been proposed to identify patients at a high risk of VTE (11-14); however, updated versions of the Caprini RAM need to be extensively validated.

We performed this single-center prospective study to identify the risk factors with the highest predictive value for postoperative VTE and evaluate the predictive value of the modified Caprini RAM in a series of patients with lung cancer undergoing resection. We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-776/rc).

Highlight box

Key findings

- The development of new additions to the modified Caprini RAM is required to improve the VTE risk assessment after lung resection.

What is known and what is new?

- Postoperative VTE is a serious complication.
- The risk-stratification approach of the modified Caprini RAM is not particularly valid after lung resection.

What is the implication, and what should change now?

- A lung resection-specific modification of the Caprini RAM is needed to evaluate the VTE risk. The combined use of multiple indicators is required to drive the development of lung cancer-specific scoring systems that improve postoperative VTE risk assessment.

Methods

Patient characteristics

We established a prospective observational study at the Department of Cardiothoracic Surgery in The First Affiliated Hospital of Chongqing Medical University from October 2019 to March 2021. Hospitalized patients with newly diagnosed lung cancer who met the following inclusion criteria were enrolled in this study: (I) without metastatic disease; (II) stages I–III; (III) underwent lobectomy, wedge resection, or segmentectomy; and (IV) age ≥18 years. The exclusion criteria were as follows: (I) long-term bedridden (stay in bed ≥1 month); (II) infection and heart failure within 1 month before admission; (III) missing records; and (IV) ongoing treatment with continuous or direct anticoagulants with vitamin K antagonists or low-molecular-weight heparin. Aspirin or clopidogrel was allowed to be taken. This prospective study was approved by The First Affiliated Hospital of Chongqing Medical University ethics committee (No. 2021-87) and complied with the tenets of the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all patients.

All patients and their families received routine preoperative education, such as performing early functional exercises and deep breathing. This was combined with a brochure and video and lecture presentations about venous thrombosis to further educate patients. Patients were advised to start with small exercises early after being awake for 2 hours following general anesthesia. Patients at low/moderate risk will accept mechanical prophylaxis. Patients with or without high bleeding risk who are at high risk will accept mechanical prophylaxis or LMWH.

Clinicopathological parameters

The clinicopathological parameters were recorded from the electronic medical record system, including age, sex, body mass index (BMI), operative time, forced expiratory volume in one second (FEV_1), preoperative hemoglobin (Hb), platelets (PLT), histological subtype [adenocarcinoma (ADC), squamous cell carcinoma (SCC), and other types], intraoperative bleeding, D-dimer, fibrin degradation product (FDP), blood transfusion, surgical approach, and type of lung resection. Hb and PLT were collected within 1 week before surgery, while D-dimer and FDP were collected on the first day postoperatively.

Identification of VTE

The primary outcome of interest was postoperative VTE, which was defined as either deep vein thrombosis (DVT) or pulmonary embolism (PE). All of the included patients were examined for VTE using imaging techniques within 1 week before surgery. Postoperative patients were examined for VTE before discharge. DVT events were confirmed using color Doppler lower extremity ultrasonography which were performed by Sonographer using Mindray ME7. PE events were confirmed by computed tomography (CT) pulmonary angiogram. Due to the postoperative transport difficulties in some patients with severe illness, bedside color Doppler lower extremity ultrasonography and cardiac ultrasound were often used as the first choice of examination in suspected patients; the former can determine the presence of DVT, and the latter can detect changes in right heart function, which indirectly suggests the presence of PE. The patients were followed up until discharge.

The modified Caprini VTE risk assessment model

In the modified Caprini score (15), clinical parameters were used to evaluate the risk of VTE, including but not limited to, age, abnormal pulmonary function, BMI, confinement to bed, major open surgery, and chemotherapy, each with an assigned weighted score ranging from 1 to 5 points, The modified Caprini scale simplifies the risk degree into three levels: 0–4 as low risk, 5–8 as moderate risk, and >9 as high risk. The modified Caprini RAM was estimated for every patient.

Statistical analysis

Continuous data were presented as mean (SD) or median (interquartile range) in case of skewness. Nominal variables were depicted as absolute numbers (%). Logistic regression analysis was performed to identify the independent risk factors for VTE. Factors with a P value <0.05 by univariate analysis were chosen as the criteria for submitting variables to the multivariate model. We used the obtained relative risk (RR) and 95% confidence interval (CI) to evaluate the association between each of the Caprini RAM categories or levels and the incidence of VTE. Receiver operating characteristic (ROC) curve analysis was conducted to determine the diagnostic performance of the modified Caprini RAM for predicting VTE using biomarkers alone and in combination with the Caprini RAM. All statistical analyses were performed using SPSS software (version 25.0; IBM Corp, Armonk, NY, USA) and GraphPad Prism software (GraphPad Software, La Jolla, CA, USA). Statistical significance was set at P<0.05.

Results

Clinical features

In total, 45 patients were excluded due to staging that did not meet the criteria, 65 due to missing clinical data, and 29 due to unavailability of imaging techniques for VTE after surgery (*Figure 1*). Finally, a total of 601 patients were included, with a VTE incidence of 10.5%. Smokers accounted for 34.9% of the participants and ADC was the most frequent histological type (86%) (*Table 1*). Patients with VTE were older than those without VTE (P<0.001). However, no statistical differences were observed in sex or BMI between both groups (P>0.05) (*Table 2*). There was no difference shown in surgical approach between two groups. No significant differences in platelet counts were found between the VTE and non-VTE groups (P>0.05). More details are shown in *Table 2*.

Among the total cohort, according to the modified Caprini score, 4.3% were in the high-risk category, 91.9% were in the moderate risk category, and 3.8% were in the low-risk category (*Table 1*). The differences between the VTE and non-VTE groups in the high-risk levels were statistically significant (P<0.001), but the differences between the two groups in the low and moderate risk levels were not statistically significant. More details are shown in *Table 2*.

Risk factors for VTE

Multivariate regression analyses showed that the following variables were statistically significant with VTE: age [odds

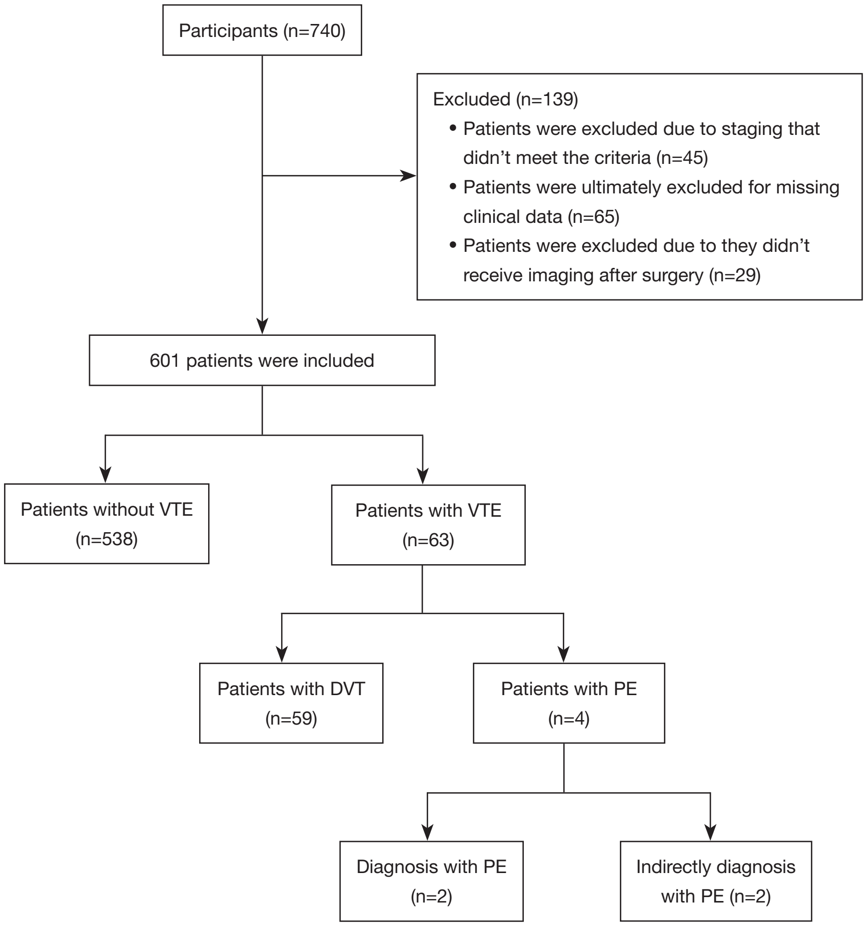

Figure 1 Study flow diagram. DVT, deep venous thrombosis; VTE, venous thromboembolism; PE, pulmonary embolism.

ratio (OR), 1.137, 95% CI: 1.083–1.193, P<0.001], Hb (OR, 1.028; 95% CI: 1.006–1.051, P=0.013), bleeding (1.002; 95% CI: 1.000–1.004, P=0.041), patient confined to bed (OR, 1.022, 95% CI: 1.007–1.038, P=0.005), and D-dimer (OR, 1.342, 95% CI: 1.222–1.473, P<0.001) (*Table 3*).

VTE risk assessment with the modified Caprini RAM

The relative risk (RR) and OR of postoperative VTE according to the modified Caprini score are displayed in *Table 4*. Compared with the modified Caprini score 0–6 group, the Modified Caprini score 7–8 group had a higher risk of VTE (RR 3.64, 95% CI: 2.23 to 5.92, P<0.001). The modified Caprini score ≥9 group had a higher risk of VTE than the modified Caprini score 0–6 group (RR 4.69, 95% CI: 2.41–9.17).

The area under the ROC curve for predicting of VTE by the modified Caprini score was 0.751 (95% CI: 0.692–0.811. P<0.001) (*Figure 2*). The sensitivity and specificity of these scores were 96.5% and 38.9%, respectively. The optimal cutoff level of the modified Caprini score was 5.5 (*Figure 2*). The ROC curve of the combined Modified Caprini score and laboratory measurements (Hb, D-dimer) showed an area under the curve (AUC) of 0.822 (95% CI: 0.760–0.855. P<0.001) (*Figure 2*).

Discussion

Our study investigated the feasibility of the modified Caprini RAM focusing specifically on lung cancer patients at high risk for postoperative VTE. In the studied cohort of patients, we observed that the incidence of VTE after lung resection was 10.5%. The incidence was independently associated with risk factors including age, Hb, bleeding, patient confinement to bed, and postoperative D-dimer. The risk degree of the modified Caprini RAM cannot

Table 1 Demographic and perioperative characteristics of patients after lung resection

Characteristic	Patients (n=601)
Age (years)	61 [53–67]
Sex	
Male	289 (48.1)
Female	312 (51.9)
Smoking history	
Yes	210 (34.9)
No	391 (65.1)
Body mass index	
Underweight (<18.5 kg/m^2)	16 (2.7)
Normal weight (18.5 to <25 kg/m^2)	402 (66.9)
Overweight (25 to <30 kg/m^2)	177 (29.5)
Obesity (≥30 kg/m^2)	6 (0.9)
History of chemotherapy	16 (2.7)
FEV_1 (L)	2.2 [1.9–2.6]
Type of lung resection	
Lobectomy	323 (53.7)
Segmentectomy	68 (11.3)
Wedge resection	210 (35)
Lymph node dissection	
Yes	460 (76.5)
No	141 (23.5)
Surgical approach	
VATS	534 (88.9)
Open	67 (11.1)
Tumor stage	
I	486 (80.9)
II	74 (12.3)
III	41 (6.8)
Histological subtype	
ADC	517 (86.0)
SCC	67 (11.2)
Other types	17 (2.8)
Intraoperative bleeding (mL)	100 [50–200]
Operative time (min)	150 [120–190]
Patient confined to bed (hours)	16 [12–23]
Blood transfusion	
Yes	29 (4.8)
No	572 (95.2)
Laboratory measurements	
Hb (g/L)	139 [130–149]
PLT (×10^9/L)	197 [11.5–240.0]
D-dimer (ng/mL)	1.6 [1.1–2.3]
FDP (mg/L)	4.1 [2.9–6.2]
Modified Caprini score	
Low risk (0–4)	23 (3.8)
Moderate risk (5–8)	552 (91.9)
High risk (≥9)	26 (4.3)

Values are mean median [interquartile range], otherwise n (%). ADC, adenocarcinoma; FEV_1, forced expiratory volume in one second; FDP, fibrin degradation product; Hb, hemoglobin; PLT, platelets; SCC, squamous cell carcinoma; VATS, video-assisted thoracoscopic surgery; VTE, venous thromboembolism.

accurately predict the risk of VTE after lung resection in our population. Thus, combining clinical biomarkers and the modified Caprini RAM score can improve VTE prediction.

The incidence of VTE in the hospitalized patients in our study was 10.05%, which is slightly higher than that reported in previous studies (3,16,17). The characteristics of the included population can significantly affect the reported rates. Population-based studies involving heterogeneous cancer sites generally report different incidence rates, and the risk of VTE varies considerably among lung cancer patients (2,18). However, the composition of the study population can significantly affect those reported rates.

We found evidence of an association between the risk of VTE and age. As a continuous variable, older age was associated with a higher risk of VTE. Supported by several

Table 2 Demographic and perioperative characteristics between the VTE and non-VTE groups

Characteristic	VTE group (n=63)	Non-VTE group (n=538)	P value
Age (years)	68 [62–73]	59 [52.8–66]	<0.001
Sex (%)			0.076
Male	37 (58.7)	252 (46.8)	
Female	26 (41.3)	286 (53.2)	
Smoking history			0.165
Yes	27 (42.9)	183 (34.0)	
No	36 (57.1)	355 (66.0)	
Body mass index			0.968
Underweight (<18.5 kg/m^2)		16 (3.0)	
Normal weight (18.5 to <25 kg/m^2)	42 (66.7)	360 (66.9)	
Overweight (25 to <30 kg/m^2)	21 (33.3)	156 (29.0)	
Obesity (≥30 kg/m^2)		6 (1.1)	
History of chemotherapy	4 (6.3)	12 (2.2)	0.066
FEV_1 (L)	2.2 [1.9–2.6]	2.2 [1.9–2.5]	0.735
Surgery resection			0.086
Lobectomy	41 (65.1)	282 (52.4)	
Segmentectomy	8 (12.7)	60 (11.2)	
Wedge resection	14 (22.2)	196 (36.4)	
Lymph node dissection			0.384
Yes	51 (81.0)	409 (76.0)	
No	12 (19.0)	129 (24.0)	
Surgical approach			0.585
VATS	56 (88.9)	478 (88.8)	
Open	7 (11.1)	60 (11.2)	
Tumor stage			0.068
I	44 (69.8)	442 (82.2)	
II	12 (19.1)	62 (11.5)	
III	7 (11.1)	34 (6.3)	
Histological subtype			0.28
ADC	49 (77.8)	468 (87.0)	
SCC	11 (17.5)	56 (10.4)	
Other types	3 (4.7)	14 (2.6)	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	VTE group (n=63)	Non-VTE group (n=538)	P value
Intraoperative bleeding (mL)	150 [100–240]	100 [50–173]	0.012
Operative time (min)	180 [140–210]	146 [115–185]	<0.001
Patient confined to bed (hours)	19 [14–43]	16 [11–22]	<0.001
Blood transfusion (%)			0.018
Yes	7 (11.1)	22 (4.1)	
No	56 (88.9)	516 (95.9)	
Laboratory measurements			
Hb (g/L)	146 [134–155]	139 [130–149]	0.012
PLT ($\times 10^9$/L)	196 [166–237]	197 [161.5–240.0]	0.931
D-dimer (ng/mL)	4.2 [1.9–9.2]	1.6 [1.1–2.3]	<0.001
FDP (mg/L)	5.2 [3.1–10.1]	4 [2.8–6.0]	<0.001
Modified Caprini score			
Low risk (0–4)	0	23 (4.3)	0.156
Moderate risk (5–8)	55 (87.3)	497 (92.4)	0.163
Other types	3 (4.7)	14 (2.6)	

Values are median [interquartile range], otherwise n (%). ADC, adenocarcinoma; FEV_1, forced expiratory volume in one second; VATS, video-assisted thoracoscopic surgery; FDP, fibrin degradation product; Hb, hemoglobin; PLT, platelets; SCC, squamous cell carcinoma; VTE, venous thromboembolism.

Table 3 Multivariable logistic regression analysis identifying risk factors for postoperative VTE

Variable	Odds ratio	95% CI	P value
Age (per 1 year increase)	1.137	1.083–1.193	<0.001
Intraoperative bleeding (per 1 mL increase)	1.002	1.000–1.004	0.041
Patient confinement to bed (per 1 hour increase)	1.022	1.007–1.038	0.005
Laboratory measurements			
Hb (per 1 g/L increase)	1.028	1.006–1.051	0.013
D-dimer (per 1 ng/mL increase)	1.342	1.222–1.473	<0.001

VTE, venous thromboembolism.

Table 4 Relative risk and odds ratio of postoperative VTE according to the modified Caprini score

Modified Caprini score	Number of patients	Patients with VTE (%)	Relative risk (95% CI), P	Odds ratio (95% CI), P
Caprini 0–6	474	31 (6.5%)	–	–
Caprini 7–8	101	24 (23.8%)	3.64 (2.23–5.92), <0.001	4.45 (2.481–7.997), <0.001
Caprini ≥9	26	8 (30.8%)	4.69 (2.41–9.17), <0.001	6.35 (2.559–15.762), <0.001

VTE, venous thromboembolism.

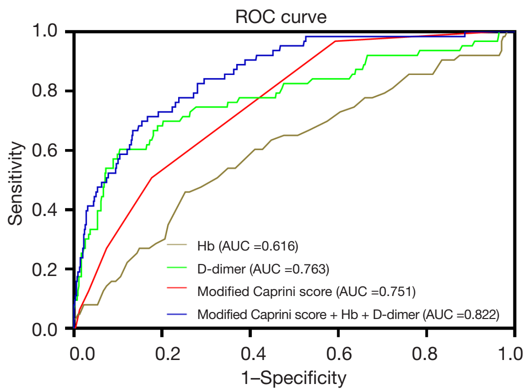

Figure 2 ROC curve analysis of the modified Caprini RAM, Hb, D-dimer, and the combination of these three predictors. The ROC curve of the combination of these three predictors showed an AUC of 0.822, 95% CI: 0.760–0.855. P<0.001. ROC, receiver operating characteristic; Hb, hemoglobin; RAMs, risk assessment models.

other reports, cancer-associated VTE frequently occurred in the older age group (18,19). Interestingly, Hayashida *et al.* (20) indicated that patients over 60 years of age had half the risk of experiencing VTE as patients <60 years of age (P<0.05). With the development of enhanced recovery after thoracic surgery (ERAS) (21), we should focus more on older patients and increase interventions to reduce the occurrence of VTE.

Several studies have indicated that D-dimer is associated with VTE in patients with cancer (19,22). Ay *et al.* found that D-dimer ≥1.44 mg/mL is shown to increase the risk for VTE (23). Fibrin D-dimer provides a measure of ongoing fibrinolysis, and elevated levels of D-dimer probably reflect the hypercoagulable state. The findings for D-dimer concentration, when assessed as a continuous variable, were consistent with our results. Presently, D-dimer seems to be one of the most promising candidates, playing a role in VTE prediction in cancer patients as well as the identification of patients who would benefit most from thrombosis prophylaxis. The advantage of the D-dimer assay is that it is routinely used in clinical practice. However, when considering D-dimer a "static" variable at a single point in time may only provide one moment of the state. Therefore, the postoperative follow-up measurement of D-dimer is paramount.

In our study, the high Hb level, as a continuous variable, was associated with increased rate of VTE, with an OR of 1.028. In contrast, Ay *et al.* showed that Hemoglobin <10 g/dL is a risk factor for VTE (23). Braekkan *et al.* (24) found that red blood cell count is a risk factor for VTE in the general population, and Hb was identified as a risk factor for VTE in their prospective, population-based study. The VTE-mechanism in this occasion, however, is debatable. A possible explanation could be that a high hematocrit or Hb could increase the concentration of platelets on the vessel wall. In combination with the low blood-flow conditions in the venous vascular system, this could lead to VTE.

A prolonged duration of surgery was also associated with an increased risk for post-discharge VTE. Thomas *et al.* (16) found that prolonged operative time was an independent predictor of VTE. In our evaluation, operative time was a risk factor for VTE in lung cancer patients. During long surgical procedures, immobility can result in increased coagulation. In addition, inflammation and oxidative stress during surgery independently contribute to thrombosis formation. For such patients, postoperative timely intervention is needed to reduce the occurrence of VTE.

There is also evidence of a probable association between the risk of VTE and bed rest time (2,18). Consistent with our results, Darzi *et al.* (18) found a slightly stronger association between immobility, defined as bed rest for >7 days, and the risk of VTE, as compared to immobility, defined as bed rest for >3 days, and the risk of VTE. Through preoperative education, patients are informed about the importance of early activities and guided to carry out early activities. Early postoperative walking should be encouraged in stable patients, while ankle pump exercises as well as flexing and extending the limbs should be performed in bed for patients who are not suitable for getting out of bed.

Intraoperative bleeding was also associated with postoperative VTE. A previous study reported that perioperative red blood cell (RBC) transfusion events increased the odds of developing postoperative VTE (P=0.018 for this trend) (25). However, we only found a statistically significant association between blood transfusion and VTE in the univariate logistic regression in our study and not in the multivariate analyses. RBC transfusion is usually performed when excessive intraoperative bleeding occurs.

According to the ROC curve, the optimal cutoff level of the modified Caprini RAM score was 5.5. Our data corroborated that D-dimer and Hb were associated with VTE, and these factors were not included in the modified Caprini RAM. Combining laboratory measurements (D-dimer and Hb) and the modified Caprini RAM can improve VTE prediction.

Our data also corroborated several risk factors that are utilized in the modified Caprini model, including older age, surgery time, and extended operative duration; however, unfortunately, the risk-stratification approach of the modified Caprini risk model could not be applied to our study population, especially in the low and moderate risk categories. Thus, based on the ROC curve analysis, we improved risk stratification and the new stratification between these two groups, achieving good results. Yet, external data are still needed for further verification.

Due to novel cancer therapies, such as targeted therapy and immunotherapy, the incidence of VTE in lung cancer patients may have changed in recent decades. Mulder *et al.* (26) found that protein kinase inhibitors, antiangiogenic therapy, and immunotherapy were important risk factors for VTE in cancer patients. The modified Caprini RAM does not include immunotherapy or targeted therapy, and perhaps more research results in the future will lead to new additions to the modified Caprini RAM.

This study has several limitations that should be noted. Firstly, although the design of our study was prospective, it did not allow us to obtain all variables that may potentially influence VTE. Secondly, the number of participants was not sufficiently large, and this was a single-center study, which may have resulted in bias. Multicentric, prospective studies with a prolonged follow-up are needed in thoracic surgical patients in China. In addition, the follow-up time for postoperative VTE is only during the patient's hospitalization, and the time window for individual studies may not be sufficient to capture all perioperative VTE events. However, we believe that, despite the mentioned limitations, our study represents a good example of the everyday clinical practice.

Conclusions

In conclusion, we identified candidate risk factors for postoperative VTE in patients with lung cancer, including age, D-dimer, Hb, bleeding, and patient confinement to bed. This study showed the risk factors in the management of VTE in lung cancer patients who will undergo resection, and will help better guidance of individual patient prophylactic management. The risk-stratification approach of the modified Caprini RAM cannot accurately predict the risk of VTE after lung resection. The combined use of multiple indicators is required to drive the development of lung cancer-specific scoring systems that improve postoperative VTE risk assessment.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-776/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-776/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-776/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-776/coif). The authors declare no conflicts of interest.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This prospective study was approved by The First Affiliated Hospital of Chongqing Medical University ethics committee (No. 2021-87) and complied with the tenets of the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all patients.

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